Clinical evaluation of preimplantation genetic diagnosis for BRCA 1/ 2 mutations

Valorization

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Introduction

Breast cancer is the third most prevalent cancer in the Netherlands.[1] In 2016, 16,640 persons (including 129 men) were diagnosed with breast cancer. This corresponds to 14% of all cancer diagnoses. In addition, 1,200 women are diagnosed with ovarian cancer yearly.[2]

Approximately 5-10% of all breast cancer cases and 10% of ovarian cancer cases are caused by a genetic predisposition, predominantly mutations in the *BRCA1* and *BRCA2* gene. The prevalence of *BRCA1/2* mutations has been estimated at 0.25-0.5%.[3] With approximately 17 million inhabitants, this can be translated to 42,500-85,000 people with a *BRCA1* or *BRCA2* mutation in the Netherlands.

Women with a pathogenic mutation in the *BRCA1* or *BRCA2* gene have a strongly increased risk of breast cancer overall and especially of breast cancer at young age. Breast cancer leads to a significant physical, psychological, and social-emotional burden on individual basis, but has also an important societal and economic impact. The available preventive options to reduce cancer risks for female carriers of a *BRCA1/2* mutation are rigorous and in particular prophylactic breast surgery is not a first-choice option for many women.[4] Surveillance strategies in order to detect breast cancer at an early stage can be very stressful and, of course, cannot prevent breast cancer. So regardless of the risk management strategy chosen, there is a burden to the patient. Female carriers of a *BRCA1/2* mutation also face an elevated risk for ovarian cancer. Ovarian cancer is often diagnosed in an advanced stage, resulting in an overall 5-year survival rate of only 40%.[2] As a consequence, ovarian cancer is referred to as 'the silent lady killer'. A risk-reducing salpingo-oophorectomy (RRSO) decreases the risk for ovarian cancer significantly in female mutation carriers when performed between the age of 35 and 45. However, this strategy induces menopause and associated health risks are the price to pay. The feasibility of a risk-reducing salpingectomy followed by a delayed oophorectomy is currently under investigation in the Netherlands (TUBA-study, Radboud University Medical Center Nijmegen).

For couples with hereditary breast and ovarian cancer (HBOC) syndrome, there are nowadays two preventive reproductive options leading to a child genetically related to both partners. Prenatal diagnosis for *BRCA1/2* mutations with pregnancy termination in case of a (female) child with the mutation is emotionally very burdensome and ethically controversial. As a consequence, it is seldomly performed in the Netherlands.[5] In the last decade, preimplantation genetic diagnosis (PGD) has become available as an alternative. Until 2016, 98 couples underwent PGD for a *BRCA1/2* mutation.[6]

Relevance of scientific results for clinical practice

Initially, PGD was only carried out for fully penetrant monogenic diseases with a young age at onset and a severe course, resulting in major burden in terms of inexorable physical disease and/or impairment and/or a significant reduction in life expectancy.[7] In subsequent years PGD was also carried out for genetic conditions leading to an increased risk of signs and symptoms later on in life, so called late onset disorders. Since 1998 PGD for Huntington's disease has been applied, a severe neurological disease with onset at adult age. The legalization of PGD for *BRCA1/2* mutations in 2008 was preceded by an intense political debate. Since the start however HBOC is one of the disorders PGD is most often applied for.[6] Both couples with a male and/or female mutation carrier can apply for PGD. Also for other cancer syndromes, such as hereditary colorectal cancer, PGD is applied regularly. This development raised issues, not only among medical professionals and third parties (e.g., politics, media) but also in affected couples. "Are hereditary cancer predisposition syndromes severe enough to justify genetic selection as applied in PGD?" "Is this the beginning of a slippery slope?" As a consequence of the shift of the application of PGD from severe early onset towards 'less severe' late onset diseases, it became more and more important that the pros of PGD prevailed the cons. In clinical practice we noticed that for many couples with a *BRCA1/2* mutation it was hard to decide whether or not to opt for PGD. In order to be able to provide more support in the challenging decision-making process, we explored the motives and considerations involved (**chapter 2**). Beside decisive intrinsic factors as the perceived severity of the condition and the couples' moral views regarding selection, several extrinsic factors were taken into account. Important extrinsic factors were the success chance of the procedure, the safety of the *in vitro* fertilization (IVF) treatment needed for PGD in terms of breast cancer risks for female mutation carriers, and the timeline of PGD and its compatibility with prophylactic surgeries in case of a female mutation carrier. Shortly after the start of PGD for HBOC a universal test for PGD of *BRCA1/2* mutations based on haplotyping was set up in our laboratory (**chapter 4**). This universal test can be applied in approximately 90% of the couples requesting PGD for a *BRCA1* or *BRCA2* mutation. For these couples, there is no longer need to develop a mutation-specific protocol. The universal PGD test enables us to offer a test within 1-2 months with a robustness conform European requirements.[8] Its availability has limited PGD work-up time and costs for test set-up and validation.

We assessed the clinical suitability of PGD for *BRCA1/2* mutations by studying (1) ovarian reserve of female mutation carriers and (2) oncological safety in terms of breast cancer risk in female mutation carriers.

Ovarian reserve is an important parameter in the prediction of the chance of pregnancy after an IVF treatment, whether or not combined with PGD.[9] Especially in PGD practice a sufficient ovarian reserve is vital since a surplus of oocytes is needed

because selection not only takes place based on embryological terms but also based on genetic test results. Several studies suggested a negative impact of a mutation in the *BRCA1* and perhaps the *BRCA2* gene on ovarian reserve. Our studies do, however, not provide evidence for a clinically relevant reduction in ovarian reserve in *BRCA1/2* mutation carriers (**chapter 6 and 7**). When assessing results of PGD treatments for *BRCA1/2* mutations in terms of pregnancy rates, these are not lower than expected in women carrying a *BRCA1/2* mutation (**chapter 3**). Consequentially, a *BRCA1/2* mutation itself should not be a reason to reject a woman from IVF (with or without PGD) treatment. Another possibility to consider for (in particularly *BRCA1*) mutation carriers may be the freezing of oocytes or embryos preceding a RRSO. The need for this option is yet unclear however and needs further investigation.
The oncological safety of the IVF treatment necessary for PGD was studied as the risk of breast cancer. We hypothesized that if there would be an adverse oncological effect, it most likely would concern the risk of breast cancer because of the involvement of estrogens in the pathophysiology of breast cancer. The association between exposure to ovarian stimulation for IVF and the incidence of breast cancer was studied in a large nationwide cohort of women with a *BRCA1* or *BRCA2* mutation. No increased risk of primary breast cancer after IVF was found (**chapter 5**). For now, there are no oncological terms on which female *BRCA1/2* mutation carriers should be dissuaded from IVF treatment (with or without PGD). However, because of the high *a priori* risk of breast cancer in these women and more limited screening options during pregnancy it is considered wise to perform additional breast screenings before the start of a new IVF treatment (with or without PGD) in female mutation carriers with breast tissue in situ.

From research to clinical practice

The research described in this thesis is not only relevant for patients faced with this matter and medical professionals involved in the care for and cure of patients with a *BRCA1/2* mutation, but also for other stakeholders such as politics. The publication of study aims and results have contributed to the awareness and knowledge of PGD for HBOC among these parties. The fact that our publication regarding the results of the first five years of clinical experience with PGD for *BRCA1/2* mutations (**chapter 3**) was selected for press release during the 28th annual meeting of the European Society for Human Reproduction and Embryology (ESHRE) in Istanbul, 2012, illustrates the newsworthiness of the findings. As a result of the growing number of professionals aware of the availability and, crucially, suitability of PGD for *BRCA1/2* mutations, patients are more often counseled about this reproductive option and, if requested, timely referred to a specialized PGD center. The insights gained into motives and considerations playing a role in the decision-making process are supportive for future couples facing this quandary. Importantly, the results are also assuring for third

parties. Although a slippery slope was feared at first, it turned out that predisposed couples do not take up PGD easily. The questions media and politicians asked in the past, are the same questions patients ask themselves. The final decision whether or not to opt for PGD is a very well-considered one in the vast majority of couples. The high number of requests of PGD for HBOC can partly be explained by the prevalence of *BRCA1/2* mutations, but also shows that predisposed couples are in need of a reproductive strategy less rigorous than prenatal diagnosis. Probably, the justification of PGD as a reproductive option for couples with a hereditary cancer predisposition syndrome can only be judged by predisposed couples themselves, since the perceived severity of the condition is one of the decisive factors in the decision-making process.
When evaluating the suitability of PGD for *BRCA1/2* mutations, our data have shown that the treatment leads to a good chance of pregnancy while the risk of breast cancer for predisposed women does not seem to increase. There is currently no need for concern in this particular group of patients.
Outcomes have been or will be published in scientific medical journals and presented at national and international congresses and expert meetings. Where appropriate, outcomes will also be presented at patient organization meetings. The conclusions will be incorporated in a decision aid (see 'Remaining questions and future plans') and discussed during PGD counseling.

Remaining questions and future plans

Our qualitative study explored motives and considerations taken into account in the decision-making process. Currently these results are further studied in a quantitative approach. Based on these results, a decision aid is developed and will be implemented in clinical practice in the near future. This digital decision aid provides information on pros and cons of PGD, prenatal testing, and conception without testing. It aims to support couples in their reproductive decision by weighing the perceived importance of each item and to uncover possible different views between both partners.
There is no convincing evidence for a clinical relevant reduction in ovarian reserve in *BRCA1/2* mutation carriers, but prospective studies on ovarian response of *BRCA1/2* mutation carriers in an IVF setting have been missing so far. A prospective study on ovarian response to stimulation for IVF/PGD is currently ongoing in our centers. Additionally, fundamental studies assessing the effect of a *BRCA1/2* mutation on oocyte and embryo quantity and quality as well as on apoptosis, as indicators for ovarian reserve are now executed in our center. It is important that future studies have the power to distinguish between *BRCA1* and *BRCA2* mutations, since these are different genetic entities with different cancer risks which may have different effects on ovarian reserve. Furthermore, the need of cryopreservation of oocytes or embryos of female *BRCA1/2* mutation carriers is presently studied.

Although the first results regarding the oncological safety of IVF in female *BRCA1/2* mutation carriers in terms of breast cancer risks are reassuring, the level of evidence is suboptimal due to study design and relatively low power. Oncological safety is further addressed by the performance of additional breast screenings before subsequent PGD treatments in female mutation carriers who still have breast tissue in situ. The necessity of these additional check-ups will be evaluated the upcoming years.

In conclusion, the research described in this thesis contributes to a responsible application of PGD for HBOC. Results may also be applicable to other hereditary cancer syndromes with a serious tumor predisposition and a high risk for offspring.

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